

that interesting work secures repetition of movements without undue fatigue. Not only must the physician take into consideration, therefore, the type of movements produced by the work which he is about to prescribe, but also the desires and interests of the patient.

We found that the soldiers in the hospital took kindly to occupational therapy, and often in spite of their disabilities produced work which from an artistic and technical point of view was of a high order. From a study of these cases over a period of more than a year it became evident that the results of this form of treatment entitle it to an important place among the therapeutic agents at our disposal in the treatment of injuries presenting paralysis, contracture, fibrosis or lack of coöordination. In view of the fact that occupational therapy has been proved to be of definite value in the treatment of various other conditions, possibly the day is not far distant when an occupational therapy department, under a trained supervisor, will be recognized as a necessary part of the equipment of every up-to-date hospital.

SOME OBSERVATIONS ON THE USE OF ARSPHENAMIN: ITS EFFECT ON THE KIDNEYS AND ITS THERAPEUTIC RESULTS.

BY HORACE B. ANDERSON, M.D.,
PENNSYLVANIA HOSPITAL, PHILADELPHIA.

RECENT medical literature is pregnant with articles either extolling the virtues of salvarsan and arsphenamin by reporting series of cases in which observations on the clinical manifestations and serologic reactions have indicated the therapeutic value of the drug or abusing and condemning the use of it by reporting all manner of reactions varying from the mild vasomotor disturbances to fatalities. It is the purpose of this paper to do neither the one thing nor the other, but rather to take the opposite ground; to submit some evidence, after studying 39 cases which have had twenty or more doses of arsphenamin, to show the non-toxic effect of the drug on the kidneys when administered in therapeutic doses over a comparatively long period of time and at the same time to give some data concerning its value as a therapeutic agent.

Concerning the gross and histopathologic changes of acute arsphenamin poisoning we have already acquired considerable information from the studies and reports of Kolmer¹ and others, but concerning the chronic poisoning we have less information largely because of the comparatively recent use of the drug. In the future, no doubt,

¹ AM. JOUR. MED. SC., 1920, cix, 188.

we will have a more accurate knowledge of the pathologic effects of its prolonged use and can come more nearly answering the important question, "What changes are produced in the kidneys by the prolonged use of arsphenamin?" One only appreciates the importance of such a question when he reflects on the fact that thousands of doses of arsphenamin are being administered every day to patients throughout the country and by the energetic application of their plans to eradicate syphilis the U. S. P. H. Service and the State boards of health are increasing daily the number of patients treated.

In this clinic prior to 1918 it was the policy to give weekly injections continuously as long as the patients would submit to it and the Wassermann reaction was positive. Since that date the policy has been to administer a course of arsphenamin consisting of six weekly injections, the dose being, unless contra-indicated, 1 decigram per thirty pounds body weight followed by a ten weeks' course of mercury in the form of the inunctions, the protoiodides or injections of the salicylate of mercury and after this a rest of one month without treatment. During the second and third year the same plan of treatment is used, but the duration of the course is modified somewhat to meet the clinical aspect of the case, the serologic findings and the mental attitude of the patient.

Wassermann tests are taken every second week while arsphenamin is being given and at the end of each course of mercury. Acetone insoluble and alcoholic extract reinforced by cholesterol antigens are used in all tests.

It was possible to study the kidney function of 39 patients who had had over twenty doses of arsphenamin. The phenolsulphone-phthalein tests were performed after the method of Rowntree and Geraghty,² the urea nitrogen, non-protein nitrogen and creatinin after the method of Folin and Wu³ and those cases that showed albumin in the urine by the heat and nitric acid tests were further tested for globulin by the use of ammonium sulphate, etc., as described by Hawk.⁴ The data of kidney function tests is given in Table I.

The average number of treatments for these 39 cases is approximately 30 doses, consisting of 4.6 decigrams each distributed over a period of a little over two years. To state it another way these patients have had an average of 14 treatments of arsphenamin per year for about twenty-six months. The preparations used have varied but in the main consisted of arsenobenzol, "Billion" arsphenamin, Metz and all later treatments have been of arsphenamin made by the Dermatological Research Laboratory of Philadelphia.

² Jour. Pharm. and Exper. Therap., 1910, i, 579.

³ Jour. Biol. Chem., 1919, xxviii, 81.

⁴ Pract. Phys. Chem., 1918, 6 ed., p. 454.

TABLE I.

Case No.	History No.	No. of doses.	No. of gms.	Duration treatment.	Present phenolphthalein output.	Qualitative urine exam. after last treatment.			Present blood examination.						
						Year.	Months.	First hour.	Second hour.	Specific gravity.	Albumin.	Casts.	Sugar.	Non-protein N.	Urea N.
1	245	32	12.0	1	7	50	18	1020	0	0	0	0	33	12	1.0
2	254	24	17.5	1	4	50	13	1020	0	0	0	0	32	15	1.8
3	281	50	20.8	4	9	55	18	1018	0	0	0	0	27	17	2.2
4	566	27	13.0	0	2	60	23	1020	0	0	0	0	33	12	1.7
5	660	52	20.0	1	7	55	18	1020	0	0	0	0	30	13	2.2
6	634	42	15.4	3	2	55	18	1012	Faint tr.	0	0	0	28	13	1.6
7	647	29	13.8	4	5	30	15	1015	0	0	0	0	46	14	2.0
8	432	26	12.9	0	0	70	15	1025	0	0	0	0	34	17.5	2.4
9	419	28	14.2	1	6	55	Lost	1020	0	0	0	0	33	16	2.0
10	370	38	15.0	2	11	65	13	1023	0	0	0	0	25	10	1.5
11	667	35	11.7	1	8	25	20	1025	0	0	0	0	31	17	1.8
12	810	44	20.0	3	9	50	20	1025	0	0	0	0	34	15	1.5
13	68	38	13.0	5	3	65	12	1010	0	0	0	0	28	12	2.3
14	431	36	15.6	3	6	60	13	1021	0	0	0	0	37	17	2.0
15	380	25	8.0	2	2	60	18	1025	0	0	0	0	32	12	1.7
16	444	20	7.7	2	2	60	13	1005	0	0	0	0	34	13	2.2
17	33	39	21.0	2	6	60	23	1012	0	0	0	0	30	14	2.8
18	37	21	12.0	1	2	60	15	1025	0	0	0	0	28	20	1.9
19	63	25	7.25	1	5	30	20	1004	0	0	0	0	27	14	1.7
20	64	32	13.4	4	2	50	10	1010	0	0	0	0	28	12	2.3
21	109	25	10.0	1	11	60	15	1015	Tr. none 2d exam.	0	0	0	31	20	2.0
22	158	45	20.0	4	5	50	20	1025	0	0	0	0	32	12	1.6
23	215	35	15.7	2	11	70	10	1015	0	0	0	0	35	13	2.0
24	220	22	9.35	..	11	55	20	1025	Very faint tr. none 2d exam.	0	0	0	37	20	1.3
25	123	33	13.2	1	9	25	15	1018	Dis. tr.; uo glob.	Lt. gr.	0	0	37	17	1.6
26	758	34	15.6	2	3	60	15	1024	0	0	0	0	33	12	1.6
27	582	31	12.8	1	3	60	10	1021	0	0	0	0	35	17	1.5
28	295	21	11.5	1	4	55	15	1020	0	0	0	0	35	17	1.7
29	595	22	11.0	2	4	30	15	1012	Cloudy, alb. and glob.	0	0	0	29	14	1.6
30	585	32	15.1	1	6	30	15	1015	0	0	0	0	20	14	1.7
31	246	34	15.5	1	11	60	15	1025	0	0	0	0	31	13	1.7
32	275	20	7.0	2	1	60	10	1015	0	0	0	0	42	15	1.6
33	232	20	0.9	1	4	60	15	1020	0	0	0	0	46	20	1.6
34	160	28	13.8	1	11	55	20	1024	0	0	0	0	40	18	1.7
35	18	23	11.5	1	..	55	10	1024	0	0	0	0	34	17	1.7
36	597	26	12.1	2	2	65	20	1020	0	0	0	0	29	13	1.7
37	656	20	10.0	1	1	55	15	1018	0	0	0	0	33	14	1.6
38	217	21	10.4	2	1	60	15	1010	0	0	0	0	37	16	1.6
39	258	20	13.4	1	3	65	10	1020	0	0	0	0	33	13	1.8

A table giving the arsphenamin received, the duration of treatment, the phenolsulphonephthalein output of the kidneys and the urine and blood examination of patients having had twenty or more doses of arsphenamin.

With the exception of patient No. 25, who was transferred from the medical clinic, where he was first seen and diagnosed tabes and nephritis, there is no conclusive proof of an existing nephritis in any of these cases. At that time and at all subsequent examinations the urine of patient No. 25 showed some casts and albumin.

His condition apparently is no worse now than when treatment was first instituted. Judging from the phenolsulphonephthalein output and the albumin and casts in the urine this patient has some nephropathy, but the evidence is in favor of its having been acquired prior to treatment. Patients Nos. 6, 21, 24 respectively show a trace of albumin at one examination, but there is no other evidence of a nephritis. Patient No. 29 shows a cloud of albumin, but when appropriate tests were used it was discerned that more than 50 per cent. of the protein precipitate was globulin. This case is well clinically, shows no other evidence of nephritis in the other examinations and therefore might be a case of non-nephritic proteinuria.

The data of table No. 1 lead in general to the conclusion that no demonstrable kidney damage has been done. There is, of course, nothing to show whether or not there has been any limitation of the wide factor of safety which the kidney naturally possesses. Several of the patients show a decreased phthalein output which one may interpret as one will.

The efficiency of any new system of treatment must be determined ultimately by the Wassermann reaction, for it has long been known that negative clinical manifestations are no guide to the patient's potential syphilitic state.

The technic employed in our laboratory for doing Wassermann tests has been modeled after that described by H. K. Detweiler.⁵ We use, however, only 0.1 c.c. of patient's serum and use the water-bath instead of dry heat for incubation. Detweiler's method of daily titrations of the complement as well as the amboceptor has proved very satisfactory. The antisheep hemolytic system is employed.

Two antigens are used, the acetone insoluble and the cholesterin reinforced alcoholic extract, made after the method described by Kolmer.⁶ These antigens are titrated every six weeks for their antigenetic and anticomplementary values. The former is tested on the pooled sera of patients who both clinically and serologically are luetic.

In our experience with cholesterized antigen it is the more sensitive and the last to become negative. The acetone insoluble is far more liable to be a correct index to the true condition when positive, but often fails to give a positive reaction in the early and late stages and also after a limited amount of treatment. This fact is demonstrated in Tables III, IV and V. Although it is true that a cholesterinized antigen will not infrequently give a false positive reaction, we believe it is the most valuable antigen that can be employed as a guide to treatment.

⁵ Am. Jour. Syph., 1918, ii, 120-137.

⁶ Inf. Immunity and Spec. Ther., 1917, 2d ed., p. 446.

TABLE II.

Case No.	Age.	Chief lesion on admission.	Duration of disease.		Stage.	Yrs. Mos.	No. of doses.	Courses of mercury.	Wassermann on admission.	Present condition.		Duration of treatment, weeks.	
			Uns.	Pro-toid.						Clinically.	Serologically.		
1	45	To be cured	9	4	Third	32	3	St. pos.	21	Well	Negative	3	
2	36	To be cured	10	4	Latent	24	4	St. pos.	0	Very much improved	Negative	4	
*3	45	Diry spells; negative Wass.; spinal fluid	10	..	Third	50	..	St. pos.	Wass. pos.	Well	Wk. pos.	16	
4	37	Ampullary sinusitis	12-13	..	Third	27	11	1	Positive	26	Well	Negative	3
*5	35	To be cured	3	..	Latent	52	1	1	St. pos.	43	Well	Negative	4
*6	39	Gumma of throat	3	..	Third	42	1	4	St. pos.	Wass. pos.	Well	Wk. pos.	0
*7	40	Osteitis	3-4	..	Third	29	3	2	Positive	20	Well	Negative	4
8	32	General adenitis	5	..	Late	26	1	8	Positive	Wass. pos.	Well; small glands	Positive	0
9	22	General weakness	7	..	Second	38	3	3	Wk. pos.	7	Well	Negative	3
*10	27	Cervical adenitis	Second	38	1	2	St. pos.	34	Well; small glands	Negative	3
11	50	Abdominal aneurysm	23	..	Third	35	2	4	St. pos.	Wass. pos.	No change	Wk. pos.	0
*12	32	Keratitis; rash	Second	44	10	10	St. pos.	4	Well	Negative	4
13	13	None	Congenital	38	St. pos.	23	Well	Negative	2
*14	50	Headache; diarrhea	10	..	Third	36	Continuous functions	29	Well	Negative	3
*15	25	Chancere	First	25	2	3	Positive	2	Well	Negative	3

16	36	Diabetes insipidus	St. pos.	..	Strong; improved	Negative	2	12	77	74
*17	37	Ulcer of penis	9	..	St. pos.	35	Well	Negative	2	12	210	75
18	35	Pharyngitis	St. pos.	..	Well	Wk. pos.	120	61
19	9	Interstitial keratitis	St. pos.	..	Well	St. pos.	72	74
20	43	Optic atrophy	St. pos.	..	Well	Negative	6	12	134	215
21	42	Leg ulcers	St. pos.	..	Well?	Wk. pos.	82	102
22	32	Mucous patches in mouth	14	..	St. pos.	20	Well?	Negative	12	24	297	228
23	34	Pain in heels	12	..	St. pos.	15	Well	Wk. pos.	157	154
24	30	?	?	..	St. pos.	16	Well	Wk. pos.	93	48
25	44	Tabes	?	..	St. pos.	17	Very much improved	Negative	5	6	132	192
26	37	Luetic sore-throat	1	..	St. pos.	9	Improved	Positive; blood and spinal fluid
*27	32	Headache; weakness	4	..	St. pos.	..	Well	Negative	5	12	156	106
*28	32	Chancere	St. pos.	..	Well	Negative	1	18	128	87
29	33	Leg ulcers	9	..	Wk. pos.	..	Well	Negative	2	14	113	54
30	40	Mycarditis; aortitis	2	..	Wk. pos.	..	Well	Negative	5	12	110	120
31	26	?	Wk. pos.	..	Well	Negative	4	30	151	177
32	30	Rash	1	..	Positive	..	Well	Negative	155	98
33	38	To be cured	Positive	..	Well	Positive	5	12	79	105
34	34	Oreana	Positive	..	Well	Positive	90	70
35	33	Rash; mucous patch	2	..	Positive	..	Well	Positive	9	14	138	98
36	31	Chancere.	Positive	..	Well	Positive	8	12	115	63
37	35	Body pains	Positive	..	Well	Positive	1	2	121	108
38	27	To be cured	Positive	..	Well	Positive	1	100	155	104
39	37	Macular eruption	Positive	..	Well	Positive	8	12	104	105
					Well	..	Well	Well	134	65

A table giving a summary of the history, treatment and present condition of the patients of Table I.

TABLE III.—IN THESE TEN CASES THE CHOLESTERINIZED ANTIGEN IS APPARENTLY MORE SENSITIVE THAN THE ACETONE INSOLUBLE ANTIGEN.

Case No.	1	2	3	4	5	6	7	8	9	10
History No.	809	P.P.	960	1050	1063	1086	1043	986	1067	1049
Lesion	Chancre.	Chancre.	Chancre.	Early secondaries.	Chancre.	Chancre.	Early secondaries.	Chancre.	Chancre.	Eruption macular.
Weekly injec. arsphenamin	Wass.	Wass.	Wass.	Wass.	Wass.	Wass.	Wass.	Wass.	Wass.	Wass.
	C.	A.	C.	A.	C.	A.	C.	A.	C.	A.
1	2	1	2	—	1	—	4	—	4	—
2	—	—	1	—	—	—	4	4	3	—
3	—	—	1	—	—	—	4	4	3	—
4	—	—	—	—	—	—	—	—	—	—
5	—	—	—	—	—	—	—	—	—	—
6	—	—	—	—	—	—	—	—	—	—
15	—	—	—	—	—	—	—	—	—	—
16	—	—	—	—	—	—	—	—	—	—
17	—	—	—	—	—	—	—	—	—	—
18	—	—	—	—	—	—	—	—	—	—

TABLE IV.—IN LATE STAGES OF SYPHILIS THE CHOLESTERINIZED ANTIGEN SEEMS TO BE MORE SENSITIVE IN SOME CASES.

Case No.	1	2	3	4	5	6	7	8	9	10
History No.	1021	1048	1019	1027	960	963	1078	951	976	1
Lesion	Latent.	Body pains.	Ulcer.	Vascular.	Latent.	Latent.	Ulcer.	Body pains.	Ulcer.	Latent.
Weekly injec. arsphenamin	Wass.	Wass.	Wass.	Wass.	Wass.	Wass.	Wass.	Wass.	Wass.	Wass.
	C.	A.	C.	A.	C.	A.	C.	A.	C.	A.
1	3	—	4	—	4	—	3	—	4	—
2	—	—	—	—	—	—	—	—	—	—
3	1	—	3	1	1	1	2	1	3	—
4	—	—	—	—	—	—	—	—	—	—
5	3	1	—	—	—	—	—	—	—	—
6	—	—	3	1	4	1	—	—	—	—
15	2	1	—	—	4	1	—	—	—	—
16	—	—	—	—	—	—	—	—	—	—
17	—	—	—	—	—	—	—	—	—	—
18	—	—	—	—	—	—	—	—	—	—
19	—	—	—	—	—	—	—	—	—	—
20	—	—	—	—	—	—	—	—	—	—

Tables giving the Wassermann reactions with acetone insoluble antigen (A) and cholesterolized alcoholic extract antigen (C). The figures 1 to 4 mean Wassermann 1 to 4 plus, — implies a negative Wassermann. The specimens of blood were taken at the time of the weekly injection of arsphenamin.

TABLE V.—UNDER TREATMENT THE CHOLESTERINIZED ANTIGEN OFTEN REMAINS POSITIVE AFTER THE ACETONE INSOLUBLE ANTIGEN HAS BECOME NEGATIVE.

Case No.	1	2	3	4	5	6	7	8	9	10
History No.	886	222	891	8	102	880	427	442	507	976
Lesion	Chancre.	Secondaries.	Spondylitis.	Secondaries.	Mucous patches.	Gumma of sternum.	Rash.	Aneurysm.	Mucous patches.	Ulcer of septum.
Weekly injection arsphenamin	Wass.	Wass.	Wass.	Wass.	Wass.	Wass.	Wass.	Wass.	Wass.	Wass.
	C.	A.	C.	A.	C.	A.	C.	A.	C.	A.
1	4	4	4	4	4	4	4	4	4	4
2	—	—	—	—	—	—	—	—	—	—
3	4	4	4	4	4	4	4	3	4	4
4	4	4	4	3	—	—	—	4	4	4
5	—	—	2	0	4	1	4	—	—	—
6	3	1	—	—	—	3	—	—	—	—
						Two months of mercury				
15	1	—	—	—	—	2	—	—	—	—
16	—	—	—	—	—	—	—	—	—	—
17	—	—	—	—	—	—	—	—	—	—
18	—	—	—	—	—	—	—	—	—	—
19	—	—	—	—	—	—	—	—	—	—
20	—	—	—	—	—	—	—	—	—	—
29	—	—	—	—	—	—	—	—	—	—
30	—	—	—	—	—	—	—	—	—	—
31	—	—	—	—	—	—	—	—	—	—
32	—	—	—	—	—	—	—	—	—	—
33	—	—	—	—	—	—	—	—	—	—

Tables giving the Wassermann reactions with acetone insoluble antigen (A) and cholesterinized alcoholic extract antigen (C). The figures 1 to 4 mean Wassermann 1 to 4 plus, — implies a negative Wassermann. The specimens of blood were taken at the time of the weekly injection of arsphenamin.

When we make a study of Table II we find 17 of the 39 cases have now had a negative Wassermann reaction for a year or more. Nine of the group have had a negative reaction for less than one year and 13 of the 39 cases continue to have weakly positive and strongly positive reactions. Of those with persistently negative reactions for a year or more 2 were in the primary stage, 4 were in the secondary and 11 in the tertiary and latent stages. The average number of doses to produce persistently negative Wassermann reactions in this group was 18.7, for those in the primary stage 12, for those in the secondary stage 12.7 and in the tertiary and latent stages 21.3 doses.

For the 39 patients the average salvarsan per patient has been 136 decigrams and the average time of treatment one hundred and seventeen weeks. This treatment has resulted in making 17 out of the 39, or 43 per cent. of the patients clinically and serologically negative for a year or more. Seven more patients, 18 per cent., have had more than two persistently negative Wassermanns, so

that, on the whole, more than half of these 39 patients already have a very favorable outlook as far as the ultimate outcome of their treatment is concerned. This 61 per cent. of the patients has had an average of 4.9 courses of six weeks of mercury in some form or other.

TABLE VI.—SECONDARY STAGE.

Case No.	History No.	Number of positive Wassermanns	Decigrams arsphenamin to first persistent negative Wassermann	Weeks to first persistent negative Wassermann	Total arsphenamin	Total weeks	Number of persistent negative Wassermanns
1	1	1	53	29	68	52	3
2	172	2	40	20	80	44	4
3	315	2	45	18	61	21	2
4	247	2	49	32	73	79	5
5	257	2	35	19	92	82	5
6	324	3	38	28	48	56	3
7	920	4	30	18	70	28	4
8	399	3	51	20	78	24	2
9	914	3	20	4	50	39	4
10	412	4	67	56	67	56	6
11	507	4	55	30	90	52	3
12	843	3	45	5	60	36	6
13	635	2	50	32	60	38	1
14	855	5	57	30	65	44	3
15	685	2	47	52	47	52	1
16	738	2	142	44	142	44	1
17	870	4	65	39	85	42	2

A table giving the arsphenamin and Wassermann records of patients starting treatment in the secondary stage. The time under observation for these patients is short and their ultimate status is still uncertain.

TABLE VII.—TERTIARY STAGE.

Case No.	History No.	Number of positive Wassermanns	Decigrams arsphenamin to first persistent negative Wassermann	Weeks to first persistent negative Wassermann	Total arsphenamin	Total weeks	Number of persistent negative Wassermanns
1	4	4	95	237	95	237	1
2	183	1	57	102	57	102	1
3	290	2	60	40	90	48	3
4	260	3	96	110	96	178	2
5	880	4	40	20	45	20	1
6	416	4	34	48	59	80	2
7	452	4	72	72	96	92	3
8	553	1	77	48	109	76	5
9	867	4	40	34	94	42	5
10	713	3	59	34	60	45	1
11	807	2	55	31	65	38	2

A table giving the arsphenamin and Wassermann records of patients starting treatment in the tertiary stage. These patients are to be classed with those of Table VI in respect to observation time.

In Tables 6 and 7, which are composed of cases now negative that presented secondary and tertiary lesions on admission, and in the majority of cases more than one positive Wassermann reaction, I believe we get a fair index as to the efficiency or inefficiency, as you may choose to call it, of our present method of treatment. The average amount of treatment necessary to produce the first persisting negative Wassermann reaction in the group of secondary

cases was 52 decigrams and the average time twenty-eight weeks. That is to say, they received 10.2 doses of arsphenamin consisting of 5 decigrams each. The average case, therefore, in this group did not give a persisting negative reaction until near the end of the second course of treatment.

It took an average of 62 decigrams to produce a persisting negative Wassermann reaction in the tertiary group. The time averaged seventy-two weeks. This means that it was during the third course of arsphenamin that they began to show a negative reaction. This at first seems better than the situation with the patients of Table II, but it is to be understood that for the patients of these latter tables more relapses may be expected. We frequently see patients who having received six to twelve doses of arsphenamin have been discharged with a negative Wassermann only to return within about a year both clinically and serologically positive.

Summary. 1. Because of its extensive use at present it is highly important that we know more perfectly the effects of the prolonged use of arsphenamin on the kidneys.

2. Kidney functional tests on 39 cases after they have received thirty doses of arsphenamin, each dose consisting of 4.6 decigrams, and distributed over a two-year period, fail to give any conclusive evidence of injury to the kidneys.

3. The efficiency of any method of treatment must ultimately be determined by the Wassermann reaction. It is more trustworthy to use at least two antigens; the acetone insoluble antigen is a safe guide to diagnosis and the alcoholic extract reinforced by cholesterin is an excellent guide to treatment.

4. It is impossible to say how much arsphenamin and how many courses of mercury may be necessary to produce a negative Wassermann reaction in any given case.

5. Six injections of arsphenamin and one course of mercury, the amount too often prescribed by certain groups of physicians, may produce one negative Wassermann reaction, but the average case of secondary or tertiary syphilis will require twelve or more doses of arsphenamin and a corresponding amount of treatment with mercury to produce a negative Wassermann reaction, and one which only with further treatment may reasonably be expected to persist.